

# The Surgical Treatment of Herpetic Keratitis

MAX FINE, M.D., San Francisco

THE REMARKABLE and menacing change which the clinical course of herpes simplex infections of the cornea has undergone in the past ten or fifteen years makes the therapy of this condition the most important therapeutic problem in ophthalmology today.

This change, as has been pointed out by such authorities as Thygeson,<sup>12</sup> Ormsby,<sup>7</sup> Gunderson (cited by Thygeson<sup>11</sup>) and others, is expressed in the increased number of cases with involvement of both eyes, the increased severity of the disease (leading to stromal necrosis and perforation in many cases), the increased frequency of chronicity and relapse, and probably an overall increase in incidence. Some observers have attributed these changes to a lowered tissue resistance to the virus brought about by the increasing use of corticosteroids. Others have expressed belief that there has been an actual change in the virulence of the herpes simplex virus, possibly associated with the widespread use of antibiotics. There are well documented reports on the occurrence of corneal perforation concomitant with the administration of corticosteroids topically or systemically. There are also cases in which recrudescence of dendritic ulcers appeared following topical steroid therapy of a disciform keratitis or a relatively inactive stromal herpetic keratitis. On the other hand, many more cases of chronic herpetic keratitis have improved after therapy with corticosteroids, and have gone on to healing. In the cases to be reported practically all the patients were treated with topical or systemic steroids under frequent and careful supervision, preparatory to keratoplasty, and in the great majority there was definite lessening of the extent and activity of the lesion, often making it possible to encompass the lesion with a smaller graft than had been anticipated. These were all cases of chronic, recurrent, herpetic keratitis—not cases of acute herpetic keratitis, in which corticosteroids are dangerous as well as ineffective. The exact role of the steroids in this disease, as well as in therapy in general, has yet to be elucidated.

There is now ample evidence that chemotherapy and antibiotics are of no value in the treatment of herpetic keratitis except for controlling the second-

• At present, corneal transplantation is the only definitive means of controlling or terminating recurrent or chronic herpetic keratitis. Of 48 keratoplastic operations for various forms of corneal herpes, 16 in quiescent cases and 32 in cases of active keratitis, all but three brought about improvement.

Recurrence of keratitis in the graft is particularly likely if the visible lesion is not excised completely and a portion of the graft border lies in contact with diseased tissue.

The mode of action of corneal transplantation in improving herpetic keratitis is not clear but several possibilities have been suggested. At least in chronic stromal herpes the removal of diseased and necrotic tissue appears to be a very important factor.

ary bacterial or fungus infections which often take place in such corneas.

At present there is no evidence that an increase in the circulating antibody titre will prevent recurrences of herpetic keratitis, or conversely, that such recurrences will give rise to an increased antibody titre.<sup>10</sup> It is therefore not likely that we may look to a vaccine or to immune sera for control of this disease. Repeated smallpox vaccination, once widely used, has not been demonstrated to be of value clinically. On experimental and laboratory grounds there is no valid basis for it, inasmuch as an increase of circulating antibody does not prevent or modify the corneal disease. On the other hand, local tissue antibodies are increased by an attack of herpetic keratitis and this increase has been shown experimentally to render the cornea relatively insusceptible to further injury by the virus, at least for a time. This may be of some importance in explaining the effects of corneal transplantation in some cases of chronic or recurrent keratitis, as will be described later.

## SURGICAL METHODS OF TREATMENT

Total removal of the infected epithelium in early cases of dendritic keratitis, or other acute forms, while the virus still appears to be limited to the epithelium appears to be the only useful method for this stage of the disease. The use of iodine, acids, alcohol or ether does not seem to add appreciably to the effectiveness of this treatment. The injudicious use of such chemical agents may even aggravate the disease by destroying the tissue-barrier to entrance of organisms into the stroma. The use of heat cautery must certainly be viewed with great caution,

Presented before the Section on Eye at the 87th Annual Session of the California Medical Association, Los Angeles, April 27 to 30, 1958.

From the Division of Ophthalmology, Department of Surgery, Stanford University School of Medicine, San Francisco, and the Veteran's Administration Hospital, San Francisco.

because of the greater tissue destruction. In cases of disciform keratitis or chronic keratitis, either superficial or deep, attempted removal of the diseased overlying epithelium seldom improves the condition and frequently makes matters worse, leaving a denuded ulcer where formerly there was none. In violent cases of dendritic keratoconjunctivitis in which most of the cornea becomes involved, the final result in terms of corneal scarring is often better if no surgical interference is attempted and the disease is permitted to run its acute course while such treatment as may be necessary to combat secondary infection or uveitis is carried on.

It is often forgotten in this era of miracle drugs and devices that a sliding conjunctival flap, or a bridge flap, will frequently lead to healing of a chronic herpetic ulcer. When such a flap is applied, it is advisable to curette away the adjacent diseased epithelium or necrotic base of the ulcer to insure adherence. Such a flap is also indicated in cases in which perforation has occurred, since it is technically difficult to use a corneal graft on the perforated globe. If indicated, the flap may be taken down at a later date and replaced with a corneal graft. Where the cornea has become very thin or a descemetocoele has appeared but has not perforated, a corneal graft is preferable.

It has been suggested that the only effective method of controlling the recurrences of herpetic keratitis would be the total removal of the entire cornea.<sup>10</sup> The complications of such treatment are certain to be worse than those of the disease. Nevertheless there are numerous cases of chronic and recurrent keratitis in which partial or subtotal corneal transplantation appears to offer therapeutic advantages.<sup>8,9</sup>

#### INDICATIONS FOR KERATOPLASTY

It has been found convenient to divide cases of herpetic keratitis in which keratoplasty is indicated into three groups: (1) Those with inactive postherpetic scars, either superficial or stromal, in which transplantation is performed primarily for optical purposes; (2) cases of prolonged recurrent episodes of superficial keratitis either diffuse or circumscribed as in metaherpetic keratitis, or deeper lesions recurring over many months or even years; (3) cases of chronic stromal keratitis which persists over many months, with or without associated uveitis leading frequently to stromal necrosis and perforation. Although, in the first group, operation is thought of as principally for improvement of vision, the increasing frequency of reactivation of apparently quiescent corneal lesions after a period of many years suggests that keratoplasty also may be considered as a prophylactic measure, the probability of recurrence being so great.

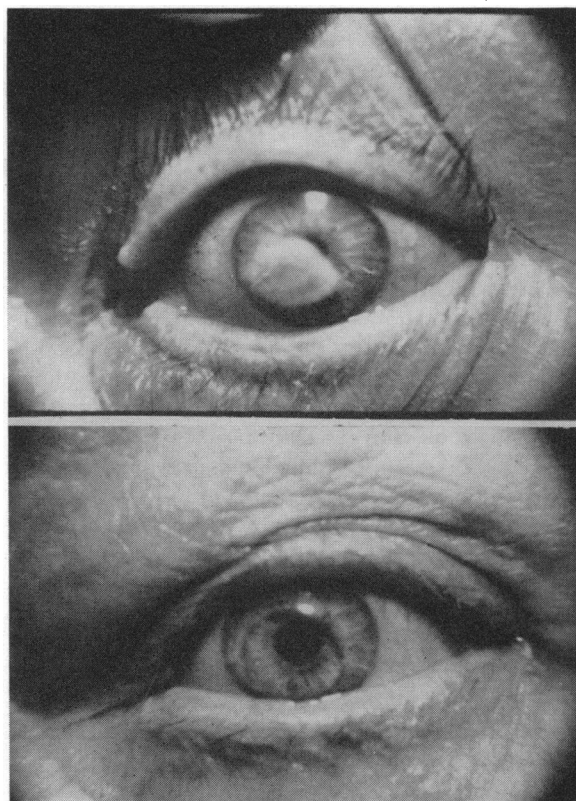


Figure 1.—Upper picture, healed disciform keratitis with calcareous degeneration. A few vessels enter the opacity from the nasal limbus. Corneal sensitivity was poor. Lower, transparent graft one year after operation. A small recurrence of keratitis appeared at the nasal side adjacent to the narrow remnant of the disciform lesion.

#### EFFECTS OF KERATOPLASTY ON HERPETIC CORNEAL LESIONS

Granted that other methods of treatment are ineffective and that replacement of the diseased tissue is the only method of therapy available at present in cases of severe chronic and recurrent herpes, how does such replacement bring about an arrest of this disastrously destructive and resistant infection? Several possibilities come to mind: The removal of diseased or necrotic tissue or perhaps removal of the infective virus. Or there may be a temporary or permanent reduction in vascularity in the area, which brings about a diminution or inhibition of the allergic reaction. It may be that introduction of fixed antibodies in the donor tissue has beneficial effect. Also to be considered is the possible biological effect of the introduction of new tissue. This concept has been supported particularly by some European investigators, notably Filatov.

#### MATERIAL OF THIS REPORT

The observations presented in this report are based upon 48 keratoplastic operations on 40 patients with various forms of corneal herpes. Sixteen

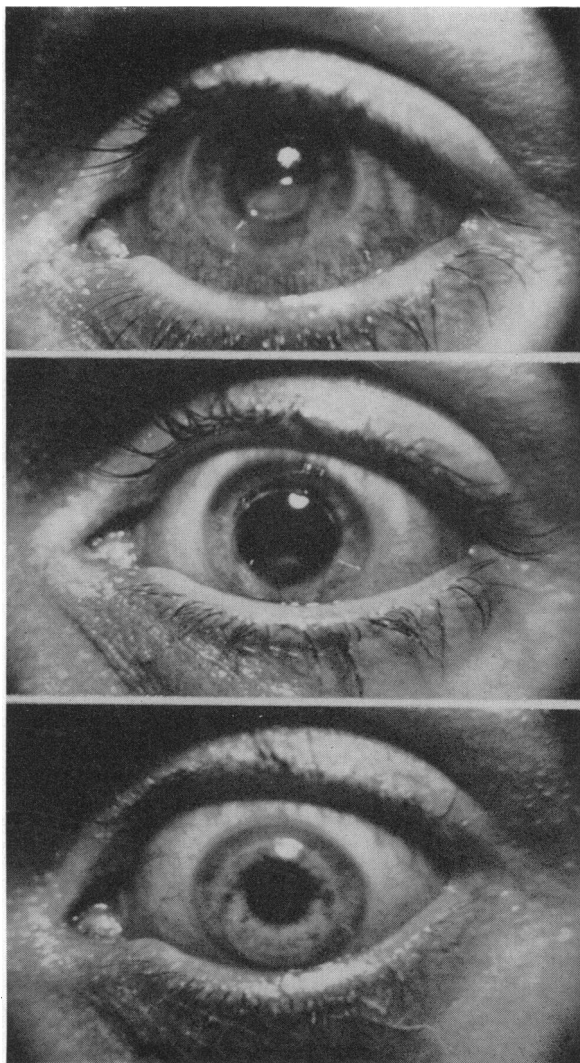


Figure 2.—*Upper*, chronic stromal herpes of six months' duration with large descemetocoele and severe iritis. *Middle*, after operation a faint opacity remained beneath the clear lamellar graft. Vision was 20/200. *Lower*, later a penetrating graft replaced the lamellar graft. Vision with correction was 20/30.

of the operations were done primarily for visual reasons. The lesions were healed, inactive, herpetic scars, either diffuse or disciform. In 15 of these 16 cases the operation was penetrating keratoplasty and in one it was lamellar. Thirty-two operations were done primarily for therapeutic reasons, that is, because of chronic or subacute herpetic keratitis which failed to heal over a period of many months, for frequent recurrences of herpetic keratitis or for necrotizing deep keratitis which threatened to perforate. Of these 32 keratoplastic operations, 22 were penetrating and ten lamellar. In many instances, of course, the designation of the transplantation as "optical" or "therapeutic" cannot be made strictly. Often both effects are intended. However, in any

case in which keratitis was not completely inactive, or in any case in which frequent recurrences had taken place up to the time of operation, the operation was classified as "therapeutic."

## RESULTS

The results in this group of 48 operations confirm the view of earlier observers<sup>6</sup> that corneal transplantation offers the only effective means of treatment at present in cases of recurrent or chronic herpetic keratitis. Even in the presence of active uveitis the operation seems to be relatively safe if proper choice of technique is made. One eye of the 40 operated upon in this series was lost, from an expulsive choroidal hemorrhage. In all but two of the remaining patients there was clinical improvement following corneal transplantation, despite the fact that there was a recurrence of keratitis following nine of the total of 48 operations. The recurrence always appeared first where the visible lesion could not be completely excised and a portion of the graft was in contact with diseased tissue. Clinical improvement may be effected even in the presence of a recurrence in the graft if no other complications appear. In one favorable case of optical keratoplasty in a healed disciform keratitis the recurrence was in the form of a dendritic ulcer, arising first in the recipient cornea and spreading into the graft. This healed without visual impairment. In the other eight the recurrence appeared as an infiltration and vascularization of the stroma near the line of union. It is noteworthy that these nine recurrences were relatively mild as compared with the preexisting keratitis, at least within the period of observation. In no instance was keratitis or uveitis aggravated by the surgical procedure. Particularly striking was the decided improvement in the inflammatory signs following keratoplasty, either lamellar or penetrating, in the patients with deep keratitis and stromal necrosis. This amelioration occurred so promptly and so regularly after operation—within 24 to 48 hours—that there could be no doubt it was a result of the procedure. The cases dealt with herein were of three orders: (1) Postherpetic opacities; (2) prolonged, recurrent, superficial keratitis with ulceration (metaherpetic keratitis) and chronic anterior stromal keratitis; (3) severe chronic stromal keratitis with necrosis.

1. The group of cases of postherpetic opacities was made up of cases in which the keratitis was completely inactive. Some of the opacities were superficial scars either diffuse or central, causing decided visual defect. Others were stromal opacities, usually disciform in type, although in some instances the disciform character of the lesion was obscured by secondary degenerative changes, such

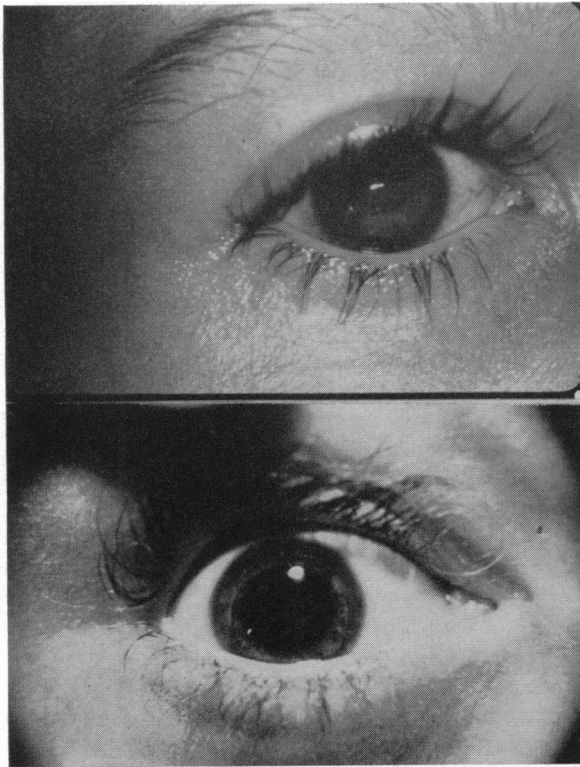


Figure 3.—*Upper picture*, chronic superficial ulceration in a 9-year-old patient following herpetic keratitis at one year of age. *Lower*, clear lamellar graft 8 mm. in diameter. As the cornea was anesthetic, condensation chamber spectacles were worn for protection.

as calcareous or fatty degeneration. Operation in these patients was performed primarily for optical purposes and it was done not less than a year after all activity had ceased. Because the objective in this group of patients was visual improvement, penetrating keratoplasty, which seems to give better visual results in properly selected cases, was carried out in all but one case, regardless of whether the opacity was superficial or stromal. The slightly greater hazard of a penetrating operation seemed warranted when the lesions were inactive. On the other hand, if keratitis is still active or uveitis is present, lamellar keratoplasty is to be preferred whenever feasible. Exceptions to this rule are (a) cases of circumscribed chronic stromal lesion which does not extend to the limbus and can be completely removed by a penetrating graft up to 7 mm. in size, and (b) cases of necrotizing deep keratitis with a prominent descemetocoele, making a lamellar graft technically very difficult. Often when lamellar keratoplasty is performed in cases of the latter kind, the descemetocoele is ruptured, making accurate coaptation of the lamellar disc difficult. If the lamellar dissection is completed without rupturing the descemetocoele, the prominence of the bulge likewise makes it diffi-

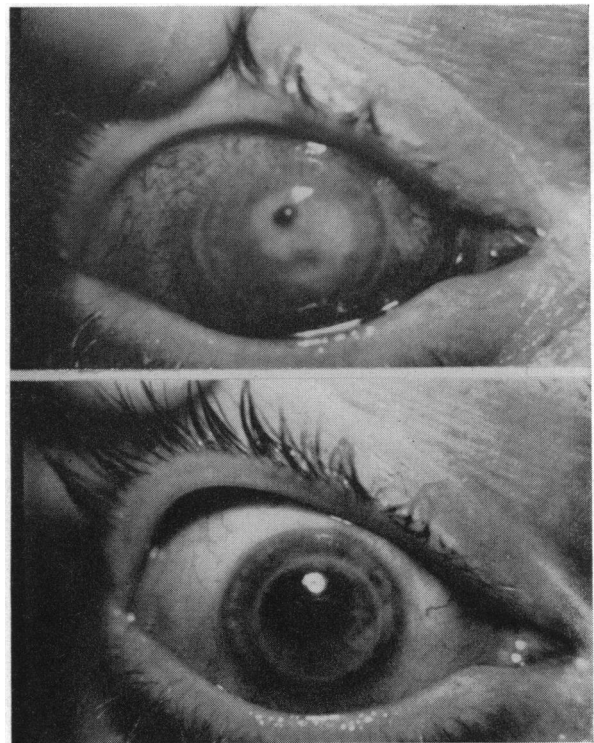


Figure 4.—*Upper picture*, chronic stromal herpes with necrosis and formation of descemetocoele. The necrotic portion of the cornea was avascular. *Lower*, an 8 mm. penetrating graft was faintly nebulous but at the time of last observation had remained unchanged for almost three years. There had been no recurrence of herpetic keratitis.

cult to achieve smooth coaptation of the graft to the underlying recipient cornea.

2. Cases of prolonged recurrent superficial keratitis with ulceration (metaherpetic keratitis) and chronic anterior stromal keratitis are the most common and the most suitable for therapeutic keratoplasty. Usually there is mild vascularization of the cornea, often with only one or two large feeding vessels, which can be coagulated at the time of the keratoplasty to minimize bleeding. In some cases the vascularity is limited to the peripheral cornea, the central portion of the cornea remaining avascular. This situation is encountered particularly in cases of superficial recurrent ulceration (metaherpetic). In the cases of this kind included in the present report the inflammatory signs were for the most part mild, the patient appearing for treatment because of recurring episodes of irritation, pain and moderate congestion. Although mild uveitis frequently accompanied these recurrences, none of the patients had sufficiently severe iritis to cause visible synechias and the pupil could be dilated in all cases.

3. Severe chronic stromal keratitis with necrosis was quite unusual before the past decade. It is now quite common, and Thygeson has pointed out the

possible relationship between the introduction of cortisone therapy and the change in the nature of disciform keratitis from a relatively benign disease to a rapidly progressing necrotizing lesion. The necrosis of the stroma may extend through Descemet's membrane, causing perforation. More frequently the resistant internal elastic membrane remains intact for a longer period and one or more descemetocoeles may appear. Severe uveitis is a frequent complication of this deep form of the disease, and hypopyon may occur. Vascularization is usually intense at the periphery of the cornea, but the central portion has few blood vessels, and often the necrosis and the sloughing of the overlying epithelium there leads to secondary infection. In the cases dealt with in this communication, removal of the necrotic corneal tissue by transplantation of cornea appeared to influence the course of the disease very promptly and very favorably. Even in cases in which the transplant did not remain completely clear, the congestion of the globe was greatly relieved, often within a few days after operation, and uveitis subsided.

655 Sutter Street, San Francisco 2.

## REFERENCES

1. Foster, J.: A case of chronic dendritic ulceration treated by a lamellar corneal graft, *Tr. Ophth. Soc. U.K.*, 70:110, 1950.
2. Franceschetti, A., and Doret, M.: *Keratoplastie á chaud*, *Ophthalmologica*, 120:11, 1950.
3. Gallenga, R.: On partial lamellar keratoplasty, *Ross. Ital. Ottal.*, 19:3, 1950.
4. Giani, P.: Late results of lamellar keratoplasty in meta-herpetic keratitis, *Ross. Ital. Ottal.*, 20:383, 1951.
5. Hobbs, H. E.: Three therapeutic lamellar grafts, *Brit. J. Ophth.*, 38:61, 1954.
6. Hogan, M. J.: Corneal transplantation in the treatment of herpetic disease of the cornea, *Am. J. Ophth.*, 43:147, (No. 4, Part II) 1957.
7. Ormsby, H. L.: Superficial forms of herpetic keratitis, *Am. J. Ophth.*, 43:107 (No. 4, Part II) 1957.
8. Paton, R. T.: *Keratoplasty*, The Blakston Division, McGraw-Hill Book Co., Inc., New York, pp. 76.
9. Paufigue, L.: The therapeutic lamellar graft, *Trans. Ophth. Soc. U. K.*, 69:67, 1949.
10. Rake, G. W.: The etiologic role of the virus of herpes simplex in ophthalmic disease, *Am. J. Ophth.*, 43:113 (No. 4, Part II) 1957.
11. Thygeson, P.: Herpes Corneae (editorial), *Am. J. Ophth.*, 36:269, 1953.
12. Thygeson, P., Kimura, S. J., and Hogan, M. J.: Observations on herpetic keratitis and keratoconjunctivitis, *Arch. Ophth.*, 56:375, 1957.

